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PPARα and Effects of TCE

We would like to offer a different opinion on the ideas presented in the article by Keshava and Caldwell (2006). The authors indicated that their article summarized scientific literature published since an earlier U.S. Environmental Protection Agency (EPA) risk assessment of trichloroethylene (TCE), with an emphasis on the possible role of proliferator-activated receptor α (PPARα) agonism relevant to TCE risk assessment. Interestingly, in the section on recent data on PPARα agonism, Keshava and Caldwell failed to establish any gene expression signature relating TCE and PPARα.

Keshava and Caldwell (2006) contended that it is difficult to identify a clear pattern of common gene expression changes for TCE and PPARα agonists in general. However, they did not consider numerous reports and reviews (e.g., Klaunig et al. 2003; Peters et al. 2005) illustrating that there are common and reproducible changes in gene expression associated with PPARα agonists. Further, extensive characterization has definitively demonstrated specific, direct targets of PPARα-retinoid X receptor heterodimers (reviewed by Klaunig et al. 2003). Keshava and Caldwell (2006) also did not discuss the possibility that the effect of TCE on gene expression could be mediated by mechanisms independent of PPARα, which likely explains the disparity described in their article. Keshava and Caldwell did not critically discuss the data summarized in their Table 2 (Keshava and Caldwell 2006), failing to note that many of these gene targets have no clear linkage with the PPARα agonist mode of action (MOA) and may be mediated either via different ligand–receptor–coactivator complexes that form on the promoter regions of the regulated genes by secondary events downstream of the initial events associated with PPARα activation, or by mechanisms that are independent of PPARα. In addition, the authors failed to describe the limitations of the various gene array platforms and to correctly interpret the findings in the context of gene targets by other PPARα agonists, especially when more comprehensive data sets exist but were not cited (Anderson et al. 2004a, 2004b).

Keshava and Caldwell (2006) further raised concerns regarding the use of PPARα-null mice to evaluate the MOA of PPARα by indicating that the physiologic differences observed in PPARα-null mice relative to wild-type mice suggest that the null mouse is an inadequate model to study the PPARα MOA. The data they cited, however, appears selective because they failed to mention that liver regeneration in PPARα-null mice is reportedly unchanged compared with wild-type mice (Rao et al. 2002), and age-related, sexually dimorphic obesity has not been observed in congenic PPARα-null mice (Akiyama et al. 2001). Thus, although the null mouse exhibits changes consistent with the critical role of PPARα in modulating fatty acid catabolism, this phenotype does not preclude its application for determining the critical role of this receptor in the MOA of PPARα agonists. Importantly, Keshava and Caldwell (2006) did not comprehensively discuss significant findings *a*) that PPARα-null mice are refractory to liver tumors induced by two different PPARα agonists (Hays et al. 2005; Peters et al. 1997); *b*) that they are refractory to increased markers of replicative DNA synthesis and suppression of apoptosis after exposure to numerous PPARα ligands (summarized by Peters et al. 2005); or *c*) that PPARα-null mice expressing the human PPARα in the liver respond to PPARα agonists by increasing expression of genes encoding proteins that catabolize lipids, but they fail to show increases in markers of cell proliferation and are resistant to liver cancer (Cheung et al. 2004; Morimura et al. 2006). To dismiss these findings through lack of discussion or citation does little to advance our understanding and suggests that Keshava and Caldwell's article is unbalanced.

Keshava and Caldwell (2006) also misrepresented an earlier review by Klaunig et al. (2003) regarding the MOA of PPARα agonists. Keshava and Caldwell (2006) incorrectly suggested that Klaunig et al. (2003) placed substantial weight on the associative event of peroxisome proliferation with this MOA, when, in fact, peroxisome proliferation was strongly—but not causally—associated, as noted for sustained increased cell proliferation. Keshava and Caldwell (2006) also misconstrued this review (Klaunig et al. 2003), focusing on DNA damage as a possible contributor to the MOA. Citing one manuscript that examined the effect of one, nonspecific PPARα ligand (DHEA) is not sufficient to refute the comprehensive review by Klaunig et al. (2003). Finally, Keshava and Caldwell (2006) also suggested that the effects of PPARα ligands on mitochondrial function are part of the MOA, but they provided no direct evidence to support their contention that PPARα agonists or TCE causes mitochondrial dysfunction.

In summary, Keshava and Caldwell (2006) missed an excellent opportunity to critically and objectively examine the data that support or refute the role of PPARα in TCE-induced effects. In our opinion, their article did not advance our understanding of the MOA of PPARα agonists or TCE.

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. Consumer Product Safety Commission.

J.C.C. is employed by Pfizer, which is developing PPAR agonists for treatment of disease indications. R.M.D. is a member of the American Chemistry Council, Phthalate Ester Panel. J.G.D. is employed by Merck Research Laboratories, which has an interest in the development of PPAR agonists as therapeutic agents, and he owns stock and stock options in Merck. R.H.M. is employed by ExxonMobil, a manufacturer of PPAR agonists (but not TCE). R.A.R. is employed by AstraZeneca, which has an active research program in PPARα/γ agonists for potential treatment of lipid and glucose abnormalities associated with diabetes. The remaining authors declare they have no competing financial interests.

James E. Klaunig
Indiana University
Indianapolis, Indiana

Michael A. Babich
U.S. Consumer Product Safety Commission
Bethesda, Maryland

Jon C. Cook
Pfizer, Inc.
Groton, Connecticut

Raymond M. David
K&D Scientific Consulting Inc.
Pittsford, New York

John G. DeLuca
Merck Research Laboratories
West Point, Pennsylvania

Richard H. McKee
ExxonMobil Biomedical Sciences Inc.
Annandale, New Jersey

Jeffrey M. Peters
The Pennsylvania State University,
University Park, Pennsylvania
E-mail: jmp21@psu.edu

Ruth A. Roberts
AstraZeneca UK
Macclesfield, Cheshire, United Kingdom

Penelope A. Fenner-Crisp
Consultant
North Garden, Virginia

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PPARα and TCE: Keshava et al. Respond

We appreciate the opportunity to discuss the issues raised by Klaunig et al. in their letter. First, we reiterate that, given the mini-monograph's scope (Chiu et al. 2006), our article (Keshava and Caldwell 2006) was intended not to comprehensively review the role of peroxisome proliferator-activated receptor α (PPARα) agonism in trichloroethylene (TCE) toxicity but rather to "highlight some of the recently published literature on PPARα ... to help inform and illustrate the key scientific issues relevant to TCE risk assessment." In addition, we considered not just hepatocarcinogenesis, but a broader range of modes of action (MOAs) and toxicity effects, necessitating a brief discussion of the article by Klaunig et al. (2003). Furthermore, because of the pending National Academy of Sciences report and revision of the TCE assessment, Klaunig et al.'s suggestion to examine whether the data "support or refute the role of PPARα in TCE-induced effects" would have been premature in the mini-monograph.

In their letter, Klaunig et al. state that there are "common and reproducible changes in gene expression associated with PPARα agonists." However, as described by Klaunig et al. (2003), the well-characterized changes are largely peroxisomal or related to lipid metabolism, and thus not causally related to hepatocarcinogenesis. Hays et al. (2005) and the Federal Insecticide, Fungicide, and Rodenticide Act Science Advisory Panel [FIFRA SAP (2004)] suggested that the MOA underlying PPARα agonist-induced hepatocarcinogenesis has not been fully elucidated in that the specific target genes modulated by PPARα leading ultimately to liver cancer have not been identified. We share the concerns of Klaunig et al. about critically interpreting gene array data and the concerns of Voss et al. (2006) about also considering dose-, time course–, species-, and strain-related differences. Given reports that PPARα agonists have zonal differences in hepatocyte, peroxisomal, and mitochondrial proliferation, and in foci development (Anderson et al. 2004a; Bannasch 1996), zone-dependent and nonparenchymal cell responses (e.g., Kupffer cells) should also be taken into account. Finally, Table 2 of our article (Keshava and Caldwell 2006) illustrated the pleiotropic and varying liver responses of the PPARα receptor to various agonists, but we did not imply that these responses were responsible for carcinogenesis.

We agree with Klaunig et al. that PPARα-null mice have been useful in investigating the MOA for hepatocarcinogenesis, particularly for the strong agonist WY-14,643 {[4-chloro-6-(2,3-xylidino)-2-pyrimidinylthiol]acetic acid}. However, possible limitations of genetically modified mice, such as lack of complete tumor development or manipulation of the carcinogenic process, should be adequately characterized [U.S. Environmental Protection Agency) (EPA) 2005]. Maronpot et al. (2004) noted the need for lifetime studies to characterize background or spontaneous tumor patterns and life spans (including those of the background strain) for these models.

PPARα-null mice have baseline difference from wild-type mice that may render them more susceptible to toxic responses [e.g., reduced glycogen stores, altered responses to fasting, elevated plasma free fatty acids, fatty liver, impaired gluconeogenesis, significant hepatic insulin resistance (Lewitt et al. 2001)], or potentially shorten their life spans with chemical exposure (Anderson et al. 2004b; Hays et al. 2005) or with further genetic modification (Nohammer et al. 2003). A comparison of their life spans with those of background strains without treatment has not been reported. Moreover, in PPARα-null mice, Wheeler et al. (2003) reported alteration of cyclin-dependent kinase/cyclin complexes necessary for cell cycle progression and DNA synthesis, whereas Voss et al. (2006) found increased apoptosis and decreased mitosis with fumonisin treatment. Thus, the question remains whether PPARα-null mice may have different susceptibility to hepatocarcinogenesis not specific to the proposed PPARα MOA.

Furthermore, bioassay study designs need adequate sensitivity to detect carcinogenic responses or elucidate MOAs. Morimura et al. (2006) and Hays et al. (2005) used high concentrations (with mortality), few (and differing numbers of) animals in treated versus control groups, and differing periods of exposure (all ≤ 1 year) complicating study interpretation. Interestingly, in the "humanized" PPARα-null mouse after 44 weeks of treatment, Morimura et al. (2006) noted (along with decreased toxicity) a WY-14,643–induced adenoma resembling spontaneous tumors rather than those seen in PPARα agonist-treated wild-type mice; no tumors were observed in controls. This raises the question of whether, if tested for longer periods of time, the humanized mice might show significant responses with tumors more consistent with those induced by a variety of non-PPARα agonists and those observed in humans (Bannasch 1996; Su and Bannasch 2003).

We acknowledge the importance of Peters et al. (1997) demonstrating *in vivo* effects of WY-14,643 on replicative DNA synthesis– and hepatocarcinogenesis–involved PPARα activation. Furthermore, we agree that peroxisome proliferation per se is an associative rather than causal event in the MOA for hepatocarcinogenesis (described by Rusyn et al. 2000). However, Klaunig et al. (2003) proposed a "minimal set of data elements" to support their PPARα MOA in rodents that consists of "PPARα agonism combined with light- or electron-microscopic evidence of peroxisome proliferation" or other markers of peroxisome proliferation. In addition, Klaunig et al.'s claim that we (Keshava and Caldwell 2006) misconstrued their review (Klaunig et al. 2003) as focusing on DNA damage as a possible contributor to the MOA is incorrect; that hypothesis was discussed by Reddy and Rao (1989). We believe it is important to identify changes both specific to PPARα activation and related to carcinogenesis.

Voss et al. (2006) reported fumonisin-induced apoptosis, cell proliferation, gene changes, and liver lesions to be PPARα-independent but having some common target genes with PPARα agonists. Thus, we should not only understand a particular agent's effects on the cell cycle and proliferation but also establish dependence on PPARα. Another issue is the applicability of

the proposed MOA across PPARα agonists. Hays et al. (2005) noted that much of the literature on the PPARα MOA used WY-14,643, which induces sustained cell proliferation, whereas weaker agonists produce more transient responses (Marsman et al. 1988). Kraupp-Grasl et al. (1990) noted differences among agonists in their abilities to promote tumors and suggested that they should not necessarily be considered a uniform group. Finally, the discussion of the effects of PPARα agonists on mitochondrial function in our article (Keshava and Caldwell 2006) was intended to raise the issue for further investigation.

Similar issues with respect to PPARα have been discussed by recent scientific panels (FIFRA SAP 2004; U.S. EPA Science Advisory Board 2006). We believe that our article (Keshava and Caldwell 2006), Klaunig et al.'s letter, and this response help to further elucidate these complex issues for the assessment of TCE as well as other chemicals.

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.

The authors declare they have no competing financial interests.

Nagalakshmi Keshava
Weihsueh A. Chiu
Jane C. Caldwell
U.S. Environmental Protection Agency
Washington, DC
E-mail: keshava.nagu@epa.gov

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Aspartame Not Linked to Cancer

In an article published in the March 2006 issue of *Environmental Health Perspectives* (*EHP*) Soffritti et al. (2006) of the European Ramazzini Foundation of Oncology and Environmental Sciences (ERF) reported that aspartame was associated with an increase in lymphomas and leukemias, transitional cell carcinomas of the renal pelvis and urether, malignant schwanomas of peripheral nerves, and hyperplasia of the olfactory epithelium.

After the publication of the ERF aspartame study (Soffritti et al. 2006), the European Commission asked the European Food Safety Authority (EFSA) to assess the ERF aspartame carcinogenicity study results as a matter of high priority following the publication (EFSA 2005). The EFSA's Scientific Panel on Food Additives, Flavorings, Processing Aids and Materials in Contact with Food (AFC), an 18-member panel that consisted of independent regulatory scientists and toxicologists, assessed the ERF aspartame carcinogenicity study using not only the ERF publication but also more extensive primary data and reports provided by ERF (EFSA 2006). Concurrently, the U.K. Food Standards Agency requested the opinion of the U.K. Committee on Carcinogenicity of Chemicals in Food, Consumer Products and Environment (COC) on the quality, analysis, and interpretation of the results of the ERF aspartame carcinogenicity study (Soffritti et al. 2006).

After a lengthy evaluation process, on 5 May 2006, the EFSA published a 44-page report (EFSA 2006). A summary comment of the EFSA report on ERF study included the following:

> The increased incidence of lymphomas/leukaemias reported in treated rats was unrelated to aspartame, given the high background incidence of chronic inflammatory changes in the lungs and the lack of a positive dose–response relationship. … The slight increase in incidence of these tumours in rats fed aspartame is considered to be an incidental finding of the ERF study and can therefore be dismissed. (EFSA 2006)

> The preneoplastic and neoplastic lesions of the renal pelvis, ureter and bladder occurring primarily in female rats along with renal calcification were most probably treatment-related, at least at the higher doses. It is widely accepted that the effect is a high dose effect of irritant chemicals or chemicals producing renal pelvic calcification as a result of imbalances in calcium metabolism, specific to the rat. The Panel considers that these effects are of no relevance for humans. (EFSA 2006)

> The data on total malignant tumours do not provide evidence of a carcinogenic potential of aspartame. … [T]he aggregation of all malignant tumour incidences or all malignant tumour-bearing animals for statistical purposes is not justified, given that, as explained above, the lymphomas/leukaemias and the renal tumours should have been excluded from the analysis. (EFSA 2006)

> Concerning the malignant schwannomas, … the numbers of tumours were low, the dose–response relationship, while showing a positive statistical trend in males, was very flat over a wide dose range and there is also uncertainty about the diagnosis of these tumours. … [T]his finding can only be fully evaluated following a histopathological peer-review of all relevant slides related to the nervous system in the ERF study and if necessary also from the historical controls. (EFSA 2006)

Furthermore, the COC's March 2006 minutes on the publication of the ERF aspartame study (Soffritti et al. 2006) concluded,

> … [I]n view of the problems in the design of the study and some concerns about the microbiological status of the colony, it was not possible to draw conclusions about the potential carcinogenicity of aspartame from the results.

The study by Soffritti et al. (2006) has major flaws that bring into question the validity of the findings. Its publication in *EHP* is not without consequence to the reputation of the National Institute of Environmental Health Sciences or to the health of the U.S. public. Publication of invalid and misleading research results relating to products such as aspartame, which can be of benefit in the battle against obesity and have a history of safe use, are a disservice to the tax-paying citizens of the United States.

The author is employed by Ajinomoto USA, which sells aspartame.

Eyassu G. Abegaz
Aginomoto Corporate Services LLC
Washington, DC
E-mail: abegaze@ajiusa.com

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Aspartame: Soffritti Responds

As communicated in his letter, Abegaz represents Ajinomoto Corporate Services LLC. Ajinomoto, which holds 45% of the market share for worldwide aspartame production (Ajinomoto 2006), is well known for its aggressive and effective defense of its commercial interests. The action by Abegaz to reproduce portions of the opinion issued by the European Food Safety Authority (2006) regarding the results of our long-term carcinogenesis bioassay on aspartame (Soffritti et al. 2006) is clearly specious.

The author declares he has no competing financial interests.

Morando Soffritti
European Foundation of Oncology and Environmental Sciences "B. Ramazzini"
Cesare Maltoni Cancer Research Center
Bologna, Italy
E-mail: crcfr@ramazzini.it

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Children's Health/Regional Collaboration to Reduce Lead Exposure in Children

As Safi et al. (2006) discussed, environmental contamination does not stop at international boundaries. An excellent example of a collaborative effort to address regional environmental exposures is that of the public health communities in Israel, Jordan, and the Palestinian Authority to assess and limit lead exposure of young children. Their dedication to this project in the face of significant political upheavals and episodic violence has demonstrated a remarkable commitment among international public health colleagues to improve environmental public health.

Safi et al. (2006) underscored the three most important strategies to prevent lead exposure in young children. First, eliminate leaded gasoline. In countries where this strategy has been successfully implemented, blood lead levels have significantly decreased (Pirkle et al. 1994; Schnass et al. 2004). More than 50 nations have eliminated lead in gasoline, and many others will initiate phase-outs over the next few years (Landrigan 2002).

Second, identify other consequential sources of lead and take action to control or eliminate them. Smelting remains a prevalent hazard in many parts of the world (ATSDR 1999). Efforts such as recycling batteries in controlled facilities have been successful in some countries.

Third, expand surveillance to ensure that recurrent or new sources of lead exposure are identified and that appropriate actions are taken. Both children and exposure sources travel. In the United States, we have found that the risk of lead exposure is much higher among immigrants when they arrive in the United States, usually as a result of use of lead-containing products; this elevated risk for exposure continues after immigrants relocate when the children are exposed to lead in paint and house dust (CDC 2005).

This collaborative project in the Middle East is an outstanding model for other international efforts to control environmental contaminants in complex regional settings. Safi et al. (2006) have shown tremendous vision, integrity, and commitment to public health under very difficult circumstances.

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Mary Jean Brown
Division of Emergency and Environmental Health Services
National Center for Environmental Health
Centers for Disease Control and Prevention
Atlanta, Georgia
E-mail: mjb5@cdc.gov

Henry Falk
Coordinating Center for Environmental Health and Injury Prevention
Centers for Disease Control and Prevention
Atlanta, Georgia

Howard Frumkin
National Center for Environmental Health
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention
Atlanta, Georgia

References

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Editor's note: In accordance with journal policy, Safi et al. were asked whether they wanted to respond to this letter, but they chose not to do so.

Flawed Ethics Recommendations of the U.S. EPA's Human Studies Review Board

The U.S. Environmental Protection Agency's (EPA) new rule to protect human research subjects has generated scientific, ethical, and legal controversy (Burton 2006). Addressing pesticide studies submitted by third parties to the U.S. EPA for possible use in regulatory decisions, the rule also authorized an independent Human Subjects Review Board (HSRB) to evaluate these studies. How successful has the HSRB been?

The board's first report (HSRB 2006), a scientific and ethical review of third-party,

intentional human-exposure studies on eight active ingredients used in pesticides, was issued 26 June 2006. The HSRB (2006) concluded that studies of seven pesticides [aldicarb, amitraz, azinphos-methyl, dichlorvos (DDVP), ethephon, methomyl, and oxamyl] "failed to fully meet the specific ethical standards prevalent at the time the research was conducted …" (see also Lockwood 2004; Needleman et al. 2005; Oleskey et al. 2004; Sass and Needleman 2004). Nevertheless, the HSRB (2006) concluded that

> There was no clear and convincing evidence that the research [on these seven pesticides] was fundamentally unethical—intended to seriously harm participants or that informed consent was not obtained.

This second HSRB conclusion is ethically questionable on several grounds. First, it relies on an arbitrary definition of "fundamentally unethical" research as either intended to seriously harm participants or that fails to obtain informed consent. Yet neither the U.S. EPA (2006) nor the National Research Council (NRC 2004) defines "fundamentally unethical" so narrowly. Instead, both say only that studies which intend harm or violate consent are examples of "fundamentally unethical" research.

In reducing "fundamentally unethical" research to only two types of problems, the HSRB excludes much behavior that ethicists traditionally have condemned. Negligence and culpable ignorance (Aristotle 1985)—as well as lying, using people as means to an end, or pursuing self-interest at the expense of others (Kant 1964)—are unethical, even without intent to harm others.

To assume that bad intentions are required to make serious harms fundamentally unethical also ignores "errors of omission" and focuses merely on commission—having harmful intent. Yet researchers err through omission if they behave irresponsibly toward their subjects: Perhaps they intend no harm, but through laziness, greed, or carelessness (Aristotle 1985), they fail to recognize subjects' manifesting harmful symptoms.

The second HSRB conclusion also imposes an unfair burden on research victims or opponents, requiring them to establish researchers' intentions. Yet intentions are almost impossible to know; they are private—not empirical—and thus typically known only by the individual. Proof of intent to harm is not required to judge bank robbers or white-collar criminals. Why should evaluators of research have such an unfair burden?

One reason for the HSRB's questionable ethical conclusions may be inadequate bioethics expertise. No board members have terminal degrees in bioethics or even ethics. Fields represented are anesthesiology, environmental health sciences (2), epidemiology, medicine, microbiology, neurology, pharmacology (3), psychology, statistics (2), and toxicology (3) (HSRB 2006). The U.S. EPA also has not followed recommendtions of its Science Advisory Board (2000), the NRC (2004), and the Environmental Medicine Workgroup (Oleskey et al. 2004) to establish specific ethics guidelines for all U.S. EPA-related research. Without such guidelines (e.g., avoid low-power studies), questionable ethical conclusions likely will continue.

The author is a member of the U.S. EPA Science Advisory Board; all opinions expressed in this correspondence are those of the author, not the U.S. EPA.

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Kristin Shrader-Frechette
Department of Biological Sciences,
Department of Philosophy
University of Notre Dame
Notre Dame, Indiana
E-mail: kshrader@nd.edu

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